PATENT
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Warren M. Zapol et al. Art Unit: 3307
Serial No. : 08/353,508 Examiner: A. Lewis
Filed : December 9, 1994
Title : METHODS AND DEVICES FOR TREATING PULMONARY VASOCONSTRICTION AND ASTHMA

Assistant Commissioner for Patents
Washington, DC 20231

DECLARATION UNDER 37 CFR 1.131

1. We are the coinventors of the subject matter of the above-referenced application. We are also the coinventors on the predecessor applications from which the above-referenced application claims priority under 35 USC §1.120: USSN 07/767,234 and USSN 07/622,865. The latter is referred to below as the "parent application".

2. Attached are copies of five pages (numbered 10, 11, and 33-35) of a draft of the parent application. This draft was prepared in Boston, Massachusetts, by attorneys for the General Hospital Corporation (owner of the above-referenced application and the parent application), and was faxed to one of us (Warren Zapol) at his office in Boston on November 21, 1990, as evidenced by the fax machine date at the top of each page. The pages numbered 33-35 include draft claims corresponding to what are claims 16-21, 31-36, 69-73, and 75 in the present application. The pages numbered 10 and 11 provide further evidence that the presently claimed device was fully conceived by us by the time the draft application was prepared. This establishes that we had conceived of the invention in the United

Date of Deposit March 19, 1997
I hereby certify under 37 CFR 1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C. 20231.
Mary E. Bowzer

States before November 21, 1990, which is just prior to the November 26, 1990, filing date of Thompson et al., U.S. Patent No. 5,187,305.

3. Completion of the application was diligently pursued by us and the attorneys between the November 21, 1990, date of the draft application and the date the completed application was filed. Attorney billing records for this application indicate that work was carried out in the course of preparing this application on each of the following dates in 1990: November 21, 26, 27, 28, and 29, and December 3, 4, and 5. The application was filed in the U.S. Patent and Trademark Office on December 5, 1990.

Declarants further state that all statements made herein of their own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date

Warren M. Zapol

1997 March 4

Date

Claes Frostell

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2/13/97
Date

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Date

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hospital where delivery occurred to one with an intensive care unit.

When an NO-releasing compound is inhaled in solid or liquid form, the particles or droplets are deposited throughout the respiratory system, with larger particles or droplets tending to be deposited near the point of entry (i.e., in the mouth or nose) and smaller particles or droplets being carried progressively further into the respiratory system before being deposited in the trachea, bronchi, and finally the alveoli. (See, e.g., Hounam & Morgan, "Particle Deposition", Ch. 5 in Respiratory Defense Mechanisms, Part 1, Marcel Dekker, Inc., NY; ed. Brain et al., 1977; p. 125.) A particle/droplet diameter of 10 μm or less is recommended for use in the method of the invention. Where pulmonary vasoconstriction is the target condition, particle/droplet size should in general be of a size distribution appropriate for deposition in the alveoli (i.e., averaging less than 5 μm, with an ideal size around 1-3 μm), while treatment of an asthma attack, which affects mainly the bronchi, would preferably be accomplished using an inhaled particle/droplet size of approximately 2-8 μm. Determination of the preferred carrier (if any), propellant, design of the inhaler, and formulation of the NO-releasing compound in its carrier are well within the abilities of those of ordinary skill in the art of devising routine asthma inhalation therapies. The portable inhaler could contain either a canister of compressed NO, preferably in an inert carrier gas such as N_2, or it could contain an NO-releasing compound either mixed in dry form with a propellant or held in a chamber separate from the propellant, or mixed with a liquid carrier capable of being nebulized to an appropriate droplet size, or in any other

configuration known to those skilled in portable inhaler technology. A few of the several types of inhaler designs that have been developed to date are discussed in, for example, U.S. Patent Nos. 4,667,668; 4,592,348; 4,534,343; and 4,852,561, each of which patents is herein incorporated by reference.

Since NO which enters the bloodstream is rapidly inactivated by combination with hemoglobin, the vasodilatory effects of inhaled NO are limited to those blood vessels near the site of NO passage into the blood stream: i.e., pulmonary microvessels. Therefore, an important advantage of the pulmonary vasodilating method of the invention is that one can selectively treat pulmonary hypertension without producing a concomitant lowering of the systemic blood pressure to potentially dangerous levels. The invention allows for effective reversal of pulmonary hypertension without the risk of underperfusion of vital organs, venous pooling, ischemia, and heart failure that may accompany systemic vasodilation. Such isolated pulmonary vasodilation is also important in treating PPHN in newborn infants, as systemic vasodilation aggravates the undesired mixing of oxygenated and de-oxygenated blood through the ductus arteriosus or the foramen ovale of newborns. Furthermore, asthma (accompanied or not by pulmonary vasoconstriction) can be safely treated by the method of the invention without risk of inducing pulmonary hypotension, as inhaled NO has been found to vasodilate only vasoconstricted blood vessels, and not blood vessels of normal tone.

The invention also advantageously provides a simple, rapid, non-invasive method of diagnosing those forms of chronic pulmonary hypertension which will be responsive to NO inhalation therapy. These patients may benefit from long-term inhalation therapy by the method of the invention,

15. The method of claim 1, wherein said gaseous nitric oxide is inhaled in the absence of tobacco smoke.

16. A method for treating pulmonary vasoconstriction in a mammal, which method comprises causing said mammal to inhale a therapeutically-effective amount of a nitric oxide-releasing compound.

17. The method of claim 16, wherein said compound is selected from the group consisting of S-nitroso-N-acetylpenicillamine, S-nitrosocysteine, nitroprusside, nitrosoguanidine, glyceryl trinitrate, isoamyl nitrite, inorganic nitrite, azide, and hydroxylamine.

18. The method of claim 17, wherein said compound is inhaled in an aerosolized form.

19. The method of claim 18, wherein said aerosolized form comprises droplets less than 10μm in diameter, said droplets comprising said compound in a suitable biologically-compatible liquid carrier.

20. The method of claim 17, wherein said compound is inhaled in powder form comprising particles less than 10μm in diameter.

21. The method of claim 16, wherein said mammal is a human.

22. A method for treating asthma in a mammal, which method comprises causing said mammal to inhale a therapeutically-effective dose of gaseous nitric oxide.

23. The method of claim 22, wherein said mammal is a human.

24. The method of claim 22, wherein said gaseous nitric oxide is inhaled in the absence of tobacco smoke.

25. A method for treating asthma in a mammal, which method comprises identifying a mammal in need of such treatment, and causing said mammal to inhale a therapeutically-effective amount of a nitric oxide-releasing compound.

26. The method of claim 25, wherein said compound is selected from the group consisting of S-nitroso-N-acetylpenicillamine, S-nitrosocysteine, nitroprusside, nitrosoguanidine, glyceryl trinitrate, isoamyl nitrite, inorganic nitrite, azide, and hydroxylamine.

27. The method of claim 26, wherein said compound is inhaled in an aerosolized form.

28. The method of claim 27, wherein said aerosolized form comprises droplets less than 10μm in diameter, said droplets comprising said compound in a suitable biologically-compatible liquid carrier.

29. The method of claim 26, wherein said compound is inhaled in powder form comprising particles less than 10μm in diameter.

30. The method of claim 25, wherein said mammal is a human.

31. A device suitable for the treatment of pulmonary vasoconstriction or asthma, said device comprising a portable inhaler containing pressurized nitric oxide gas.

32. A device suitable for the treatment of pulmonary vasoconstriction or asthma, said device comprising a metered-dose inhaler containing a nitric oxide-releasing compound.

33. The device of claim 32, wherein said compound is in powder form.

34. The device of claim 32, wherein said compound is dissolved or suspended in a biologically-compatible liquid carrier.

35. The device of claim 33, wherein said compound is selected from the group consisting of S-nitroso-N-acetylpenicillamine, S-nitrosocysteine, nitroprusside, nitrosoguanidine, glyceryl trinitrate, isoamyl nitrite, inorganic nitrite, azide, and hydroxylamine.